

FORM PTO-1390 (REV. 11-2000)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER 3893-0139P	
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371				U.S. APPLICATION NO. (If known, see 37 CFR 1.5) <div style="font-size: 1.5em; font-weight: bold;">10/030970</div>	
INTERNATIONAL APPLICATION NO. PCT/DK00/00387		INTERNATIONAL FILING DATE July 11, 2000		PRIORITY DATE CLAIMED July 16, 1999	
TITLE OF INVENTION AMINO BENZOPHENONES AS INHIBITORS OF IL-1 β AND TNF- α					
APPLICANT(S) FOR DO/EO/US OTTOSEN, Erik Rytter					
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:					
<ol style="list-style-type: none"> 1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1). 4. <input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) <ol style="list-style-type: none"> a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau). (WO 01/05751) b. <input checked="" type="checkbox"/> has been transmitted by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). <ol style="list-style-type: none"> a. <input type="checkbox"/> is transmitted herewith. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4) 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)). <ol style="list-style-type: none"> a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> have been transmitted by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). 					
Items 11. to 20. below concern document(s) or information included:					
<ol style="list-style-type: none"> 11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98, Form PTO-1449(s), and International Search Report (PCT/ISA/210) with 1 document(s). 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A FIRST preliminary amendment. 14. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 15. <input type="checkbox"/> A substitute specification. 16. <input type="checkbox"/> A change of power of attorney and/or address letter. 17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825. 18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4). 19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4). 20. <input checked="" type="checkbox"/> Other items or information: <ol style="list-style-type: none"> 1.) PCT/IPEA/409 w/ Amended Sheets 2.) Zero (0) sheets of formal drawings 					

U.S. APPLICATION NO (if known, see 37 CFR 1.5)

10/030970

INTERNATIONAL APPLICATION NO

PCT/DK00/00387

ATTORNEY'S DOCKET NUMBER

3893-0139P

21. ☒ The following fees are submitted:**BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):**

Neither international preliminary examination fee (37 CFR 1.482)
nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO
and International Search Report not prepared by the EPO or JPO. \$1,040.00

International preliminary examination fee (37 CFR 1.482) not paid to
USPTO but International Search Report prepared by the EPO or JPO \$890.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO
but international search fee (37 CFR 1.445(a)(2)) paid to USPTO. \$740.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO
but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00

International preliminary examination fee (37 CFR 1.482) paid to USPTO
and all claims satisfied provisions of PCT Article 33(1)-(4). \$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =

Surcharge of **\$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30
months from the earliest claimed priority date (37 CFR 1.492(e)).

CALCULATIONS PTO USE ONLY

\$ 890.00

\$ 130.00

CLAIMS**NUMBER FILED****NUMBER EXTRA****RATE**

Total Claims 10 - 20 = 0 X \$18.00 \$ 0.00

Independent Claims 1 - 3 = 0 X \$84.00 \$ 0.00

MULTIPLE DEPENDENT CLAIM(S) (if applicable) YES + \$280.00 \$ 280.00

TOTAL OF ABOVE CALCULATIONS =

\$ 1300.00

☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are
reduced by 1/2.

SUBTOTAL =

\$ 1300.00

Processing fee of **\$130.00** for furnishing the English translation later than ☐ 20 ☐ 30
months from the earliest claimed priority date (37 CFR 1.492(f)). +

TOTAL NATIONAL FEE =

\$ 1300.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be
accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +

TOTAL FEES ENCLOSED =

\$ 1300.00

Amount to be:
refunded \$
charged \$

a. ☒ A check in the amount of \$ **1300.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account. No. _____ in the amount of \$ _____ to cover the above fees.
A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any
overpayment to Deposit Account No. 02-2448.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to:

Birch, Stewart, Kolasch & Birch, LLP or Customer No. 2292

P.O. Box 747

Falls Church, VA 22040-0747

(703) 205-8000

Date: January 15, 2002

By

Andrew D. Meikle, #32,868

/ka

PATENT
3893-0139P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: OTTOSEN, Erik R.
Int'l. Appl. No.: PCT/DK00/00387
Appl. No.: NEW Group:
Filed: January 15, 2002 Examiner:
For: AMINO BENZOPHENONES AS INHIBITORS OF
IL-1 β AND TNF- α

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION

Assistant Commissioner for Patents
Washington, DC 20231

January 15, 2002

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/DK00/00387 which has an International filing date of July 11, 2000, which designated the United States of America and was published in English.--

IN THE CLAIMS:

Please amend the claims as follows:

3. (Amended) A compound according to claim 1 or 2 wherein R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, methyl, or methoxy.

4. (Amended) A compound according to claim 1, wherein R_1 is methyl and R_2 is Cl.

6. (Amended) A pharmaceutical composition containing as an active ingredient a compound according to claim 1 together with a pharmaceutically acceptable carrier and optionally together with a second active ingredient optionally selected from the group consisting of glucocorticoids, vitamins D's, anti-histamines, platelet activating factor (PAF) antagonists, anticholinergic agents, methyl xanthines, β -adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

7. (Amended) Use of a compound according to claim 1 for the preparation of a medicament for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory

bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, osteoporosis and acne.

8. (Amended) A method for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, osteoporosis and acne, characterised in administering to a patient suffering from at least one of said diseases an effective amount of one or more compounds according to claim 1 as an active ingredient alone, or if necessary together with a pharmaceutically acceptable carrier, and, optionally, a second active ingredient optionally selected from the group consisting of glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticholinergic agents, methyl xanthines, β -adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

9. (Amended) A method of treatment according to claim 1 comprising administering to a mammal in need of systemic treatment a suitable dose of a compound of formula I of from 0.1 to 200 mg/kg

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bodyweight, preferably a dose of from 0.2 to 50 mg/kg of mammal
bodyweight one or more times daily.

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REMARKS

The specification has been amended to provide a cross-reference to the previously filed International Application.

The claims have been amended to remove the improper multiple dependencies.

Attached hereto is a marked-up version showing the changes made to the application by this Amendment.

Entry of the above amendments is earnestly solicited. An early and favorable first action on the merits is earnestly solicited.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By 

Andrew D. Meikle, #32,868

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3893-0139P

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Attachment: VERSION WITH MARKINGS TO SHOW CHANGES MADE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims have been amended as follows:

3. (Amended) A compound according to [any one of the preceding claims] claim 1 or 2 wherein R₁ represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, methyl, or methoxy.

4. (Amended) A compound according to [any one of the preceding claims] claim 1, wherein R₁ is methyl and R₂ is Cl.

6. (Amended) A pharmaceutical composition containing as an active ingredient a compound according to [any one of claims 1 to 5] claim 1 together with a pharmaceutically acceptable carrier and optionally together with a second active ingredient optionally selected from the group consisting of glucocorticoids, vitamins D's, anti-histamines, platelet activating factor (PAF) antagonists, anticholinergic agents, methyl xanthines, β -adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

7. (Amended) Use of a compound according to [any one of claim 1 to 5] claim 1 for the preparation of a medicament for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, osteoporosis and acne.

8. (Amended) A method for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, osteoporosis and acne, characterised in administering to a patient suffering from at least one of said diseases an effective amount of one or more compounds according to [any one of claims 1 to 5] claim 1 as an active ingredient alone, or if necessary together with a pharmaceutically acceptable carrier, and, optionally, a second active ingredient optionally selected from the group consisting of glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticholinergic agents, methyl xanthines, β -adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum

cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

9. (Amended) A method of treatment according to [the preceding claim] claim 1 comprising administering to a mammal in need of systemic treatment a suitable dose of a compound of formula I of from 0.1 to 200 mg/kg bodyweight, preferably a dose of from 0.2 to 50 mg/kg of mammal bodyweight one or more times daily.

AMINO BENZOPHENONES AS INHIBITORS OF IL-1 β AND TNF- α

FIELD OF THE INVENTION

This invention relates to a hitherto unknown class of compounds which shows anti-inflammatory effects, to pharmaceutical preparations containing these compounds, to dosage units of such preparations, and to their use in the treatment and prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis and atopic dermatitis, uveitis, septic shock, AIDS, and acne.

BACKGROUND OF THE INVENTION

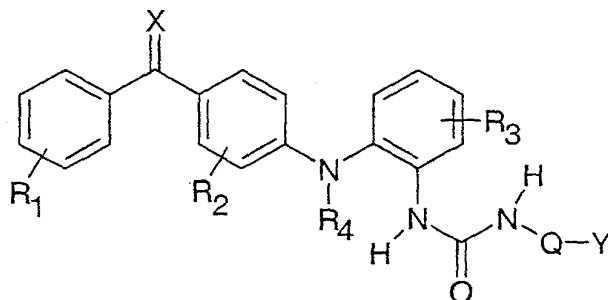
Previously, a series of closely related aminobenzophenones (e.g. 4-(2-amino-4-nitrophenylamino)benzophenone) have been described (Hussein, F.A. *et al*, Iraqi J. Sci., 22, 54-66 (1981)). However, there is no description of their uses. PCT/DK98/00008 discloses aminobenzophenone inhibitors of interleukin 1 β (IL-1 β) and tumour necrosis factor α (TNF- α) secretion *in vitro*, said compounds being potentially useful for treatment of inflammatory diseases in which the production of cytokines is involved in the pathogenesis, e.g. asthma, rheumatoid arthritis, psoriasis, contact dermatitis, and atopic dermatitis. Furthermore the compounds of PCT/DK98/00008 was tested *in vivo* for anti-inflammatory properties in the 12-O-tetradecanoylphorbol-13-acetate (TPA) induced murine chronic skin inflammation model, (De Young, L.M. *et al*, Agents Actions, 26, 335-341 (1989); Carlson, R.P. *et al*, Agents Actions, 17, 197-204 (1985); Alford, J.G. *et al*, Agents Action, 37, (1992); Stanley, P.L. *et al*, Skin Pharmacol, 4, 262-271 (1991)). In this chronic skin inflammation model the compounds had the same potency compared to the reference compound hydrocortisone.

The purpose of the present invention is to provide further pharmacologically active aminobenzophenone derivatives and related compounds.

This purpose is achieved with the novel aminobenzophenone derivatives according to the general formula I that are potent inhibitors of interleukin 1 β (IL-1 β) and tumour necrosis factor α (TNF- α) secretion *in vitro*, making them potentially useful for treatment of inflammatory diseases, in which the secretion and regulation of cytokines or more specifically interleukin 1 β (IL-1 β) and tumour necrosis factor α (TNF- α) are involved in the pathogenesis. The inhibition or down regulation of the cytokines is possibly due to an inhibition of MAP kinases.

SUMMARY OF THE INVENTION

The compounds of the present invention are represented by the general formula I below



I

wherein R_1 and R_2 independently represent one or more, same or different substituents selected from the group consisting of halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3) alkyl, (C_2-C_3) olefinic group, (C_1-C_3) alkoxy, (C_1-C_3) alkylthio, (C_1-C_6) alkylamino, (C_1-C_3) alkoxycarbonyl, cyano, carbamoyl, phenyl, and nitro; R_2 further being represented by hydrogen;

R_3 represents hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3) alkyl, (C_2-C_3) olefinic group, (C_1-C_3) alkoxy, (C_1-C_3) alkylthio, (C_1-C_6) alkylamino, (C_1-C_3) alkoxycarbonyl, phenyl, cyano, carboxy, or carbamoyl;

R_4 represents hydrogen, (C_1-C_3) alkyl, or allyl;

Q represents a bond, $-SO_2-$, or $-C(R_6)(R_7)(-O-C=O)-$, in which formula R_6 and R_7 independently represent hydrogen, trifluoromethyl, or (C_1-C_4) alkyl;

Y represents (C_1-C_{15}) alkyl, (C_2-C_{15}) olefinic group, (C_3-C_{10}) carbocyclic group, or phenyl, any of which is optionally substituted by one or more, same or different substituents represented by the formula R_5 ; or Y represents a group of formula $-(Z-O)_n-Z$, where Z is a (C_1-C_3) alkyl and n is an integer > 1 , and no continuous linear sequence of atoms in the group Y exceeds 15;

R_5 represents halogen, hydroxy, mercapto, trifluoromethyl, (C_1-C_4) alkyl, amino, $(C_1-$

C₃)alkoxy, (C₁-C₃)alkylthio, (C₁-C₆)alkylamino, (C₁-C₃)alkoxycarbonyl, cyano, azido, nitro, -COOH, -CONH₂, -CONHR', or -CONRR' wherein R and R' stands for (C₁-C₃)alkyl;

X represents oxygen or sulphur,

or a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof.

DETAILED DESCRIPTION OF THE INVENTION

10 Preferred embodiments of the invention:

In compounds of the invention it is preferred that R₁ represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C₁-C₂)alkyl, (C₂-C₃)alkenyl, (C₁-C₃)alkoxy, (C₁-C₃)alkoxy-carbonyl, or cyano; R₂ represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C₁-C₂)alkyl, (C₂-C₃)alkenyl, (C₁-C₃)alkoxy; R₃ represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, (C₁-C₃)alkyl, (C₂-C₃)alkenyl, (C₁-C₃)alkoxy, (C₁-C₃)alkoxycarbonyl, cyano, or carboxy; R₄ represents hydrogen, (C₁-C₂)alkyl, or allyl; X represents oxygen; Q represents a bond. or -SO₂-; Y represents (C₁-C₆)alkyl; (C₂-C₆)alkenyl; (C₃-C₆)cycloalkyl; (C₅-C₈)cycloalkene group; or phenyl; any of which is optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R₅ as defined below, and R₅ represents fluoro, chloro, bromo, hydroxy, amino, (C₁-C₂)alkoxy, (C₁-C₄)alkylamino, (C₁-C₃)alkoxycarbonyl, cyano, azido, -COOH, -CONH₂, -CONHR', or -CONR'R' wherein R' represents (C₁-C₂)alkyl.

More preferred are compounds of formula I wherein R₁ represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, methyl, or methoxy; preferably R₁ is methyl and most preferably 2-methyl; R₂ represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, methyl, or methoxy; preferably R₂ is Cl and most preferably 2-Cl; preferably R₃ represents hydrogen, methyl, methoxy, fluoro, chloro, or bromo; R₄ represents hydrogen; Y represents (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, or

phenyl; any of which may be optionally substituted by one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, amino, azido, (C₁-C₃)alkyl, (C₁-C₂)alkoxycarbonyl, cyano, -COOH, -CONH₂, and CON(CH₃)₂.

Most preferably Y represents methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, cyclohexyl, hexyl, 6-chloro-hexyl, -(CH₂)₂COOCH₂CH₃, (CH₂)₂COOH, tolyl, or phenyl.

Further preferred compounds of general formula I are compounds wherein R₁, R₂, and R₃ represent one substituent. R₁ and R₂ preferably being in the ortho position.

Specific compounds of the invention includes:

1-Cyclohexyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 101),

1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 102),

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-phenylurea (Compound 103),

1-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 104),

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(4-methylphenylsulfonyl)urea (Compound 105),

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(phenylsulfonyl)urea (Compound 106),

1-*tert*-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 107),

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-*iso*-propylurea (Compound 108),

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-propylurea (Compound 109),

1-Methyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 110),

Ethyl 3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionate (Compound 111),

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 112),

3-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionic acid (Compound 113),

1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-5-fluoro-phenyl]urea (Compound 114),

1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-*N*-methyl-phenylamino]-5-fluoro-phenyl]urea (Compound 115),

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-*n*-butyl-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 116),

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,5-dimethylbenzoyl)-phenylamino]phenyl]urea
(Compound 117),

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(3-chloro-2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 118),

5 1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-ethoxy-2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 119),

1-Ethyl-3-[5-bromo-2-[3-ethoxy-4-(2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 120),

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-chloro-2-methylbenzoyl)-phenylamino]phenyl]urea
10 (Compound 121),

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,3-dimethylbenzoyl)-phenylamino]phenyl]urea
(Compound 122),

1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(4-methoxy-2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 123),

15 1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,4,5-trimethylbenzoyl)-phenylamino]phenyl]urea
(Compound 124),

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-fluoro-2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 125),

1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea
20 (Compound 126),

and salts thereof with pharmaceutically acceptable acids, hydrates or solvates thereof.

As used in the specification, unless specified to the contrary, the following terms have the
meaning indicated:

25

"Alkyl" refers to any univalent group derived from an alkane by removal of a hydrogen atom from any carbon atom, and includes the subclasses of normal alkyl (*n*-alkyl), and primary, secondary and tertiary alkyl groups respectively, and having the number of carbon atoms specified, including for example (C₁-C₃)alkyl, (C₁-C₄)alkyl, (C₅)alkyl, (C₅-C₁₅)alkyl, (C₆-C₁₀)alkyl, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, and *t*-butyl. Alkane refers to an acyclic branched or unbranched hydrocarbon having the general formula C_nH_{2n+2}, and therefore consisting entirely of hydrogen atoms and saturated carbon atoms.

30

35 "Olefinic group" refers to a straight or branched acyclic hydrocarbon having one or more carbon-carbon double bonds of either E or Z stereochemistry where applicable, and having the number of carbon atoms specified. The term includes, for example, (C₂-C₁₅)olefinic

group, preferably a (C₂-C₁₅)alkenyl; (C₂-C₃)olefinic group, preferably a (C₂-C₃)alkenyl; vinyl; allyl; 1-butenyl; 2-butenyl; and 2-methyl-2-propenyl. Olefinic groups having only one carbon-carbon double bond, herein called alkenyl, are preferred.

- 5 "Alkoxy" refers broadly to a radical of the formula -OR, where R is alkyl as defined above, for example (C₁-C₃)alkoxy, (C₁-C₂)alkoxy, methoxy, ethoxy, n-propoxy, and the like.

"(C₁-C₃)alkylthio" refers broadly to a radical of the formula -SR, where R is alkyl as defined above and includes methylthio, ethylthio, n-propylthio, and 2-propylthio.

10

"(C₁-C₆)alkylamino" refers broadly to a radical of the formula -NHR or -NR₂, where R is alkyl as defined above having from 1-6 carbon atoms and includes, for example, methylamino, dimethylamino, di-(n-propyl)amino, and n-butyl(ethyl)amino.

15

"(C₁-C₃)alkoxycarbonyl" refers broadly to a radical of the formula -COOR, where R is alkyl as defined above and includes methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, and i-propoxycarbonyl.

20

"(C₃-C₁₀)monocyclic hydrocarbon group" includes the saturated cycloalkanes and unsaturated cyclic olefins, such as cycloalkenes having one endocyclic double bond, and having from 3-10 carbon atoms, and includes, for example, (C₃-C₈)cycloalkyl, cyclopropyl, cyclopentyl, cyclohexyl, and cyclooctyl, (C₃-C₁₀)cycloalkene group, and (C₃-C₈)cycloalkene group. Specific examples are cycloprop-2-enyl, cyclobut-2-enyl, cyclopent-2-enyl, cyclohex-3-enyl, and cyclonon-4-enyl.

25

"Amino" means the group -NH₂.

"Carbamoyl" refers to any one of the groups -CONH₂, -CONHR, and -CONRR' where R and R' represent alkyl as defined above.

30

"Carboxy" refers to a radical of the formula -COOH.

"Halogen" means the same or different of fluoro, chloro, bromo, and iodo; fluoro, chloro, and bromo being preferred.

35

The phenyl group of R₁ and R₂ may optionally be substituted, e.g. with hydroxy; amino;

nitro; cyano; halogen, preferably fluoro, chloro, or bromo; methyl; or methoxy.

The compounds can be used in the form of their salts which are formed with pharmaceutically acceptable inorganic or organic acids, such as hydrochloric, hydrobromic and hydroiodic acid, phosphoric acid, sulphuric acid, nitric acid, p-toluenesulphonic acid, methanesulphonic acid, formic acid, acetic acid propionic acid, citric acid, tartaric acid, succinic acid, benzoic acid, maleic acid, these examples being considered as non-limiting for the invention.

10 Pharmacological methods

To study the effect of the compound of the present invention *in vitro* the inhibition of the IL-1 β and TNF- α secretion was measured using the following procedure:

Cytokine production was measured in the media from lipopolysaccharide (LPS) stimulated peripheral blood mononuclear cells. The mononuclear cells were isolated from human peripheral blood by Lymphoprep[®] (Nycomed, Norway) fractionation and suspended in RPMI 1640 (growth medium) with foetal calf serum (FCS, 2%), at a concentration of 5×10^5 cells/ml. The cells were incubated in 24-well tissue culture plates in 1 ml aliquots. Test compounds were dissolved in dimethylsulfoxide (DMSO, 10 mM) and were diluted with the medium. Compounds were added to the cells for 30 minutes, then LPS (1 mg/ml final concentration) was added. The plates were incubated for 18 hours, and the concentration of IL-1 β and TNF- α in the medium was determined by enzyme-linked immunosorbent assays. The median inhibitory concentrations (IC₅₀) of the compounds were calculated. The results are shown in Table 1 below.

The compounds of the present invention also show similar activities in the ability to inhibit PMN (polymorphonuclear) superoxide secretion which is also indicative of potentially useful anti-inflammatory drugs. The compounds were tested using the following procedure:

Human polymorphonuclear (PMN) granulocytes were isolated from human blood by dextran sedimentation, Lymphoprep[®] fractionation and hypotonic lysis of contaminating erythrocytes.

Superoxide anion generation was measured as the superoxide dismutase inhibitable reduction of ferricytochrome C (Madhu, S.B. et al, *Inflammation*, 16, 241, (1992)). The cells were suspended in Hanks' balanced salt solution, and incubated for 10 minutes at

37°C with test compounds. The cells were primed by the addition of TNF- α (3 ng/ml final concentration) for 10 minutes, and then ferricytochrome C, (final concentration 750 μ g/ml), bovine serum albumin (BSA, final concentration 1 mg/ml) and formyl-methionyl-leucyl-phenylalanine (fMLP, final concentration 10^{-7} M) were added for 3 minutes. The cells were chilled on ice, and were spun down. The optical densities in the cell-free supernatant was measured in a spectrophotometer. The median inhibitory concentration (IC₅₀) of the compounds was calculated. The results are shown in Table 1.

Table 1.		Inhibition of cytokines and PMN-superoxide production in vitro by compounds of the present invention.		
		The median inhibition concentration (IC ₅₀ , nM) of		
Comp No.; Ex. No.		IL-1 β	TNF- α	PMN-superoxide
101, Ex. 1		13	5.0	4.0
102, Ex. 2		22	2.2	13
114, Ex. 14		7.9	3.2	4.0
ref. a)		13	7.1	5.0
ref. b)		>1000	631	316

ref. a): 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone, compound 106 disclosed in PCT/DK98/00008. ref. b): 1-Ethyl-3-[2-(4-benzoyl-phenylamino)phenyl]urea of the general formula I in PCT/DK98/00008.

These results show that the compounds of the present invention are able to inhibit the production of IL-1 β , TNF- α and PMN-superoxide showing pharmacological activities comparable to compounds of the prior art, thus making them potentially useful in the treatment of inflammatory diseases.

To study the compounds of the present invention *in vivo* the 12-O-tetradecanoylphorbol-13-acetate (TPA) induced murine chronic skin inflammation model can be used (De Young, L.M. et al, Agents Actions, 26, 335-341 (1989); Carlson, R.P. et al, Agents Actions, 17, 197-204 (1985); Alford, J.G. et al, Agents Action, 37, (1992); Stanley, P.L. et al, Skin Pharmacol, 4, 262-271 (1991)), cf. description of method in PCT/DK98/00008 hereby incorporated by reference. These results shows that the compounds of the present invention are of the same potency compared to known reference compounds, e.g. hydrocortisone with its known side effects, whereas the compounds of the present

invention are well tolerated and are non-toxic. Some members of the present class of compounds show a very low absorption, thus making them especially useful in the treatment of various dermatological diseases. In general, they may be administered by e.g. oral, intravenous, intranasal, topically or transdermal routes.

5

Method of preparation

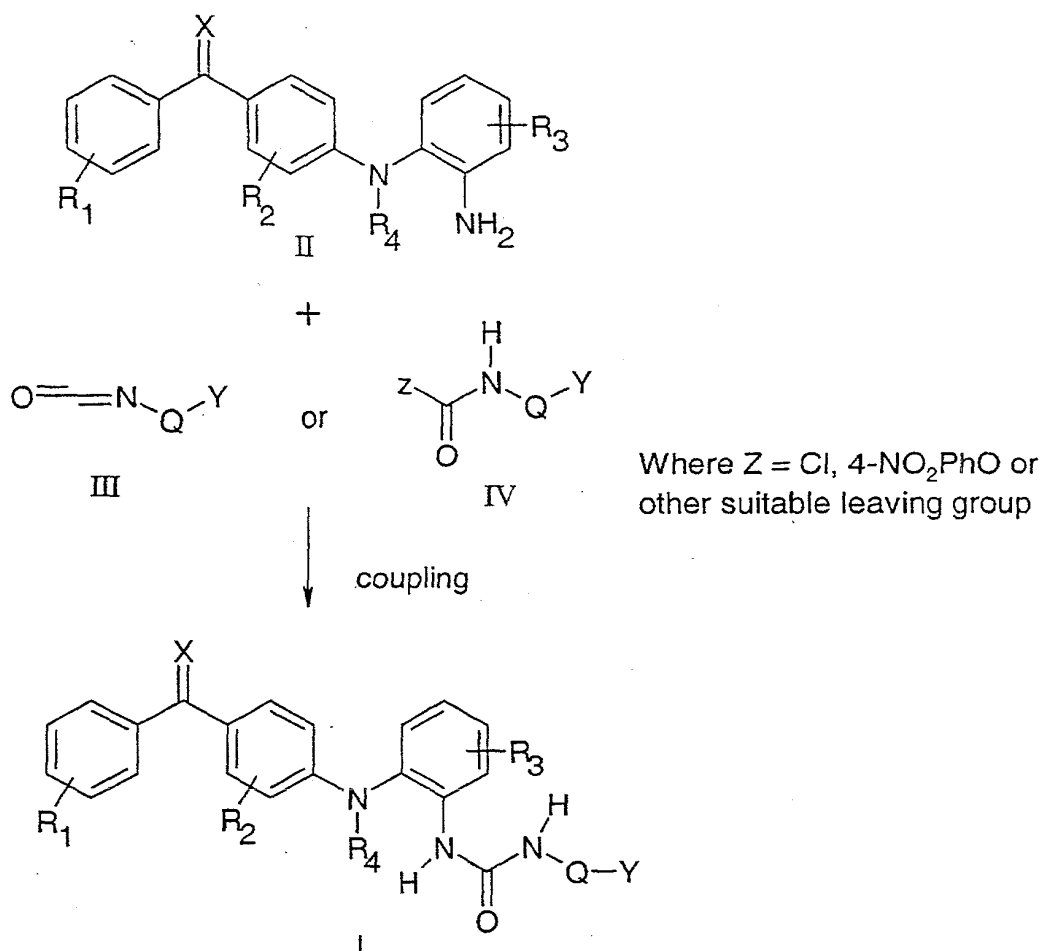
The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of organic synthesis. The compounds of the present invention can be synthesised using the methods outlined below, together with methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The novel compounds of formula I may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of experiment and work-up procedures, are chosen to be conditions of standard for that reaction, which should be readily recognised by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the educt molecule must be compatible with the reagents and reactions proposed. Not all compounds of formula I falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods can be used.

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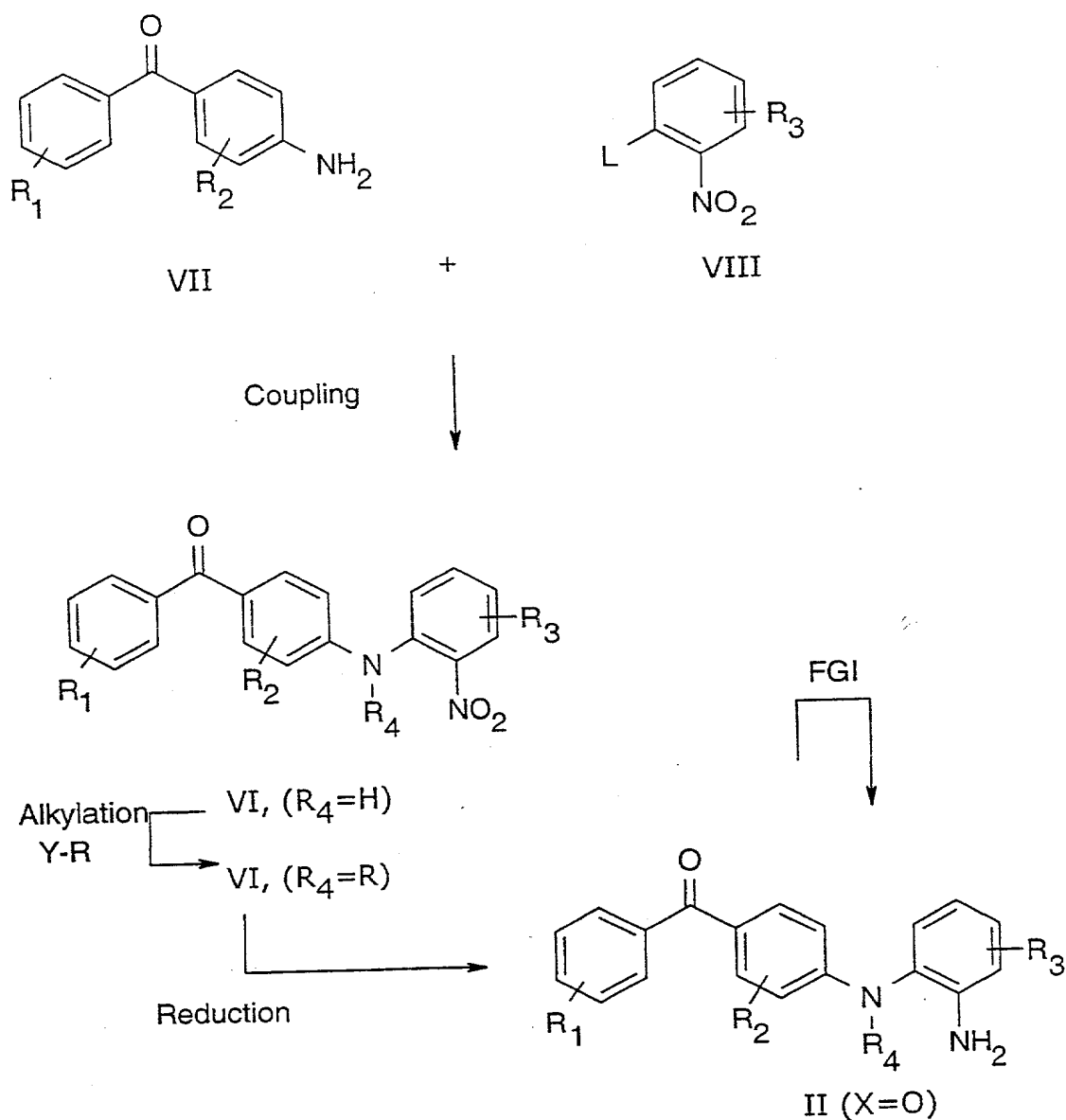
Compounds according to the present invention may be prepared by a process comprising coupling of an amine of the formula II with an isocyanates of the formula III or a suitable activated derivative with the formula IV; e.g. carbamic acid chlorides and carbamic acid esters (phenoxy, 4-nitrophenoxy and 2,4,5-trichlorophenoxy) or other suitable activated derivatives of the formula IV, as shown in scheme 1, where R_1 , R_2 , R_3 , R_4 , Q , X , and Y are as defined in general formula I, except that any substituents or functional group which are potentially reactive in the coupling reaction may themselves be protected before the coupling reaction is performed and subsequently removed.



and R_1 , R_2 , R_3 , R_4 , X , Q , and Y have the above meanings.

Scheme 1

- 5 Compounds accordingly to the present invention with the general formula II ($X=O$) may be prepared by several methods known to those skilled in the art of organic synthesis. One useful sequence is shown in scheme 2 were the key process comprising coupling of an
- 10 formula I, to give a coupled product with the general formula VI, except that any substituents or functional group which are potentially reactive in the coupling reaction may themselves be protected before the coupling reaction is performed and subsequently removed. This compound VI may then be reduced to the corresponding amine with the general
- 15 formula II by treatment with standard reducing agents. Examples of such reducing agents include, but are not limited to, stannous chloride dihydrate; hydrogen, ammonium formate, or hydrazine hydrate and a catalytic amount of palladium on carbon.



L: Br, I, OSO₂CF₃, or F and Cl

Y: Cl, Br, I, OSO₂CF₃, OSO₂CH₃, or OTs

FGI: Functional group interconversion

and R₁, R₂, R₃, and R₄ have the above meanings.

Scheme 2

- 5 The coupling reaction is carried out using any of the methods for the formation of diphenylamines known to one skilled in the art of organic synthesis. The preferred method is the nucleophilic aromatic substitution method which comprising coupling of an amine with an arylfluoride or arylchloride in the presence of a base, in a suitable solvent. Especially

potassium-*tert*-butoxide (KOt-Bu), sodium-*tert*-butoxide (NaOt-Bu), sodium hydride (NaH), and potassium hydride (KH) have proven to be the best bases in this process, but other bases may be used as well.

- 5 The reaction is typically performed at ambient temperature (20-25 °C) in dipolar aprotic solvents like dimethylsulfoxide (DMSO), dimethylformamide (DMF), or *N*-methylpyrrolidone (NMP) under an inert atmosphere like argon or nitrogen.

10 Alternatively, the coupling reaction can be done by the palladium catalysed amination method which comprising coupling of an amine with an arylhalogenide (iodide, bromide, triflate, or in some cases chloride) in the presence of a base, a suitable Pd source, and a suitable phosphine ligand in an inert solvent.

15 The palladium compound used in the process is not particularly limited, and as specific examples are

20 palladium(II) acetate, palladium(II) chloride, palladium(II) bromide, dichlorobis(triphenylphosphine)palladium(II), tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0). The preferred ligand include, but are not limited to, racemic or non-racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (hereinafter referred to as BINAP), tri-*o*-tolylphosphine, tri-*tert*-butylphosphine, 1,1'-bis(diphenylphosphino)-ferrocene, bis[(2-diphenylphosphino)phenyl]ether (DPEphos), 2-dicyclohexylphosphanyl-2'-dimethylaminobiphenyl, 2-(di-*tert*-butylphosphino)biphenyl, and 9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene (Xantphos). The amount of palladium and ligand used in this
25 process is typically in the range 0.1 to 10 % by mole relative to the amount of the aromatic halide (or triflate) used. Especially sodium-*tert*-butoxide (NaOt-Bu) and caesium carbonate (Cs₂CO₃) have proven to be the best bases in this process, but other bases may be used as well. The reaction is typically performed at elevated temperature (80-120 °C) in inert solvents like 1,4-dioxane, toluene, benzene and tetrahydrofuran under an inert
30 atmosphere like argon or nitrogen.

Compounds according to the present invention in which R₄ is not hydrogen may be prepared by a process comprising coupling of an amine of the formula VI (R₄= H) with an alkylating agent, as shown in scheme 2, where R₁, R₂, R₃, and, R₄ are as defined in
35 general formula I, except that any substituents or functional group which are potentially reactive in the coupling reaction may themselves be protected before the coupling reaction is performed and subsequently removed.

Typically alkylating agents of the general formula R-Y include, but are not limited to, iodides (Y=I), bromides (Y=Br), chlorides (Y=Cl) and sulfonates (Y=OSO₂R', where R' represents methyl, trifluoromethyl or 4-methylphenyl).

5

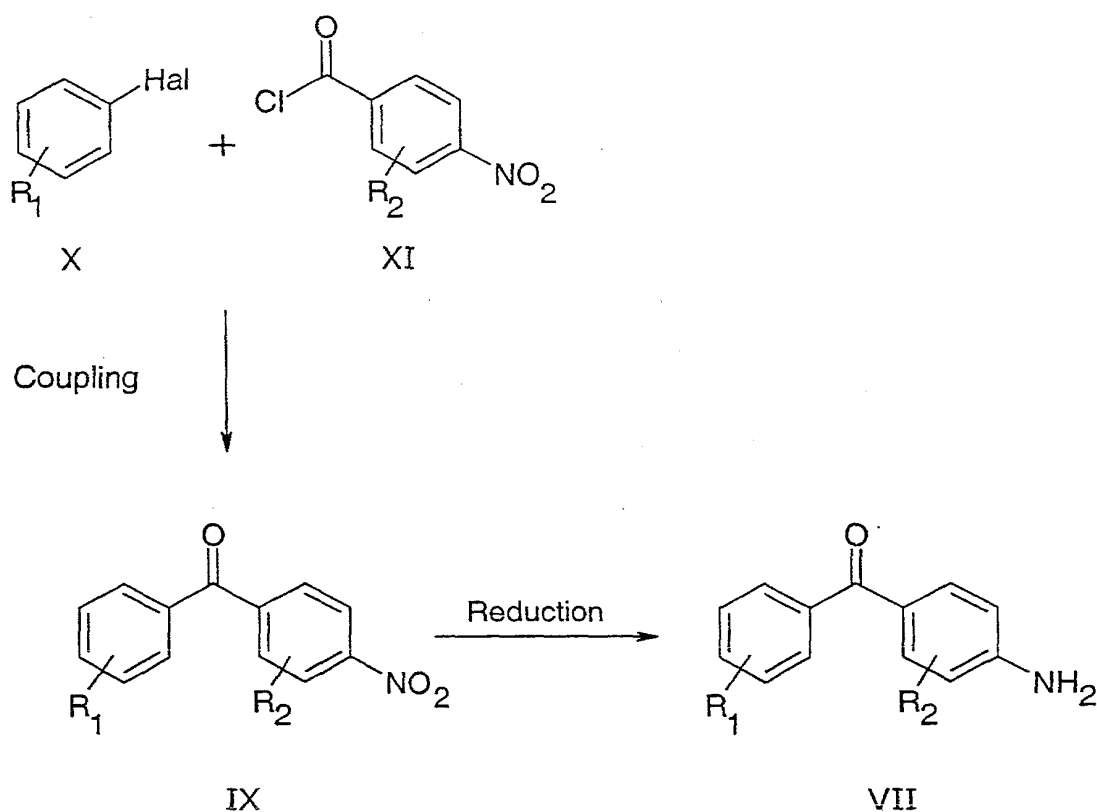
Compounds according to the present invention may in special cases be prepared by a simple functional group interconversion (FGI), meaning a standard process, known to those skilled in the art of organic synthesis, where a functional group in compounds with the general formula I (or any other intermediate described herein) is transformed into a different functional group in one or more synthetic steps, leading to a new compound with the general formula I. Examples of such processes are, but are not limited to, hydrolysis of an ester to give an acid under basic conditions; deprotection of an methylether to give an phenol by treatment with e.g. borontribromide (BBr₃); and catalytic hydrogenation of an olefin to give an saturated hydrocarbon.

10

Compounds according to the present invention in which C=X represents -(CS)- may be prepared from compounds of the invention (or any other intermediate described herein) in which C=X represents -(CO)- by a process using an appropriate thiocarbonylating agent such as phosphorous pentasulfide (P₄S₁₀), or Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide) or the like.

15

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hal: Br, I

and R_1 , and R_2 have the above meanings.

SCHEME 3

- 5 Compounds accordingly to the present invention with the general formula VII may be prepared by several methods known to those skilled in the art of organic synthesis. One useful sequence is shown in Scheme 3. The key step comprises coupling of a bromide (or iodide) with the general formula X with an acid chloride with the general formula XI to afford the benzophenone with the general formula IX. This compound IX may then be
- 10 reduced to the corresponding amine with the general formula VII by treatment with standard reducing agents. Examples of such reducing agents include, but are not limited to, stannous chloride dihydrate; hydrogen, ammonium formate, or hydrazine hydrate and a catalytic amount of palladium on carbon. The coupling reaction is done by transforming the bromide (X) into a reactive organometallic intermediate, e.g. by treatment with
- 15 butyllithium to afford the lithium derivative or by treatment with magnesium to afford the magnesium derivative. The reactivity of this intermediate is then modulated by transme-

tallation to e.g. zinc, by treatment with ZnCl_2 , ZnBr_2 , or ZnI_2 . This organozinc compound is then coupled with the acid chloride, with the general formula XI, under the influence of a palladium(0) complex in catalytic amount. Examples of such catalyst include but are not particularly limited to tetrakis(triphenylphosphine)palladium(0), tetrakis(triphenylarsine)-palladium(0), dichlorobis(triphenylphosphine)palladium(II), or benzylchlorobis(triphenylphosphine)palladium(II).

It may be more advantageous in some cases to alter the sequence of the processes described above. The described sequence of processes is not considered as being limited for the preparation of the compounds of the present invention with the general formula I and alteration of the reaction sequence is an obvious alternative for those skilled in the art of organic synthesis.

The present compounds are intended for use in pharmaceutical compositions which are useful in the treatment of the above mentioned diseases.

The amount required of a compound of formula I (hereinafter referred to as the active ingredient) for therapeutic effect will, of course, vary both with the particular compound, the route of administration and the mammal under treatment. A suitable dose of a compound of formula I for systemic treatment is 0.1 to 200 mg/kg bodyweight, the most preferred dosage being 0.2 to 50 mg/kg of mammal bodyweight, administered one or more times daily.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. Conveniently, the active ingredient comprises from 0.1% to 100% by weight of the formulation.

Conveniently, dosage units of a formulation contain between 0.07 mg and 1 g of the active ingredient. For topical administration, the active ingredient preferably comprises from 1% to 20% by weight of the formulation but the active ingredient may comprise as much as 50% w/w. Formulations suitable for nasal or buccal administration may comprise 0.1% to 20% w/w. for example about 2% w/w of active ingredient.

By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

The formulations, both for veterinary and human medical use, of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefore and optionally other therapeutic ingredient(s). The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

The formulations include those in a form suitable for oral, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular and intravenous), transdermal, intra-articular, topical, nasal, or buccal administration.

The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The active ingredient may also be administered in the form of a bolus, electuary or paste.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier such as cocoa butter, or in the form of an enema. Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredient which is preferably isotonic with the blood of the recipient.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the active ingredient for both intra articular and ophthalmic administration.

Formulations suitable for topical administration, including eye treatment, include liquid or

semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops.

- 5 Formulations suitable for administration to the nose or buccal cavity include powder, self-propelling and spray formulations, such as aerosols and atomizers.
In addition the aforementioned ingredients, the formulations of this invention may include one or more additional ingredients.

- 10 The compositions may further contain other therapeutically active compounds usually applied in the treatment of the above mentioned pathological conditions, for instance glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticholinergic agents, methyl xanthines, β -adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing
15 agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

- The novel compounds of the invention are of value in the human and veterinary practice as systemic and topical therapeutic agents for the treatment and prevention of diseases. The novel compounds show anti-acne properties and, i.a., anti-inflammatory and cytokine
20 regulating effects possibly due to MAP kinase inhibition, and are useful in the treatment and prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, and osteoporosis.

- 25 The invention will now be further described in the following general procedures, preparations and examples:

EXAMPLES

General procedures, preparations and examples

30

- The exemplified compounds I are listed in table 2. All melting points are uncorrected. For ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra (300 MHz) chemical shift values (δ) (in ppm) are quoted, unless otherwise specified, for deuteriochloroform and hexadeuterodimethylsulfoxide solutions relative to internal tetramethylsilane (δ 0.00) or chloro-
35 form (^1H NMR δ 7.25, ^{13}C NMR δ 76.81). The value for a multiplet (m), either defined (doublet (d), triplet (t), quartet (q)) or not at the approximate mid point is given unless a range is quoted (s singlet, b broad). The organic solvents used were anhydrous. The term

"chromatography" refers to column chromatography using the flash technique and was performed on silica gel.

The following abbreviations have been used throughout:

5

AgOAc	Silver acetate
BTC	Bis(trichloromethyl) carbonate
CDCl ₃	Deuteriochloroform
DMF	<i>N,N</i> -Dimethylformamide
10 DMSO-d ₆	Hexadeuterodimethylsulfoxide
Et ₃ N	Triethylamine
EtOAc	Ethyl acetate
Et ₂ O	Diethylether
HMPA	Hexamethylphosphorous triamide
15 NMM	<i>N</i> -Methylmorpholine
THF	Tetrahydrofurane
TLC	Thin layer chromatography

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Table 2 Compounds of general formula I

Comp. No.	Example No	X	R ₁	R ₂	R ₃	R ₄	Q	Y
101	1	O	2-Me	2-Cl	H	H	Bond	-cyclohexyl
102	2	O	2-Me	2-Cl	H	H	Bond	-CH ₂ CH ₃
103	3	O	2-Me	2-Cl	H	H	Bond	-phenyl
104	4	O	2-Me	2-Cl	H	H	Bond	-(CH ₂) ₃ CH ₃
105	5	O	2-Me	2-Cl	H	H	-(SO ₂)-	-tolyl
106	6	O	2-Me	2-Cl	H	H	-(SO ₂)-	-phenyl
107	7	O	2-Me	2-Cl	H	H	Bond	-C(CH ₃) ₃
108	8	O	2-Me	2-Cl	H	H	Bond	-CH(CH ₃) ₂
109	9	O	2-Me	2-Cl	H	H	Bond	-(CH ₂) ₂ CH ₃
110	10	O	2-Me	2-Cl	H	H	Bond	-CH ₃
111	11	O	2-Me	2-Cl	H	H	Bond	-(CH ₂) ₂ COOCH ₂ CH ₃
112	12	O	2-Me	2-Cl	4-Br	H	Bond	-CH ₂ CH ₃
113	13	O	2-Me	2-Cl	H	H	Bond	-(CH ₂) ₂ COOH
114	14	O	2-Me	2-Cl	4-F	H	Bond	-CH ₂ CH ₃
115	15	O	2-Me	2-Cl	4-F	CH ₃	Bond	-CH ₂ CH ₃
116	16	O	2-Me, 4-Bu	2-Cl	4-Br	H	Bond	-CH ₂ CH ₃
117	17	O	2-Me, 5-Me	2-Cl	4-Br	H	Bond	-CH ₂ CH ₃
118	18	O	2-Me, 3-Cl	2-Cl	4-Br	H	Bond	-CH ₂ CH ₃
119	19	O	2-Me, 4-OEt	2-Cl	4-Br	H	Bond	-CH ₂ CH ₃
120	20	O	2-Me	2-OEt	4-Br	H	Bond	-CH ₂ CH ₃
121	21	O	2-Me, 4-Cl	2-Cl	4-Br	H	Bond	-CH ₂ CH ₃
122	22	O	2-Me, 3-Me	2-Cl	4-Br	H	Bond	-CH ₂ CH ₃
123	23	O	2-Me, 4-OMe	2-F	4-Br	H	Bond	-CH ₂ CH ₃
124	24	O	2-Me, 4-Me, 5-Me	2-Cl	4-Br	H	Bond	-CH ₂ CH ₃
125	25	O	2-Me, 4-F	2-Cl	4-Br	H	Bond	-CH ₂ CH ₃
126	26	O	2-Me	2-F	4-Br	H	Bond	-CH ₂ CH ₃

The numbering in Table 2 refers to the numbering in the formula below

5 To a solution or suspension of an amine (1.0 mmol), with the general formula II, in an inert solvent (10 ml, typically toluene, pyridine or EtOAc) was slowly added an isocyanate (1.1-2.5 mmol), with the general formula III. Stirring was continued at room temperature for 24 h or until the starting material had disappeared as seen on TLC. The reaction mixture was concentrated *in vacuo* to afford the crude product. The crude product was typically either purified by chromatography and/or crystallized to give the title compound.

15 General procedure: 1

¹H NMR (DMSO-d₆): δ 8.34 (s,1H), 8.05 (d,1H), 7.76 (s,1H), 7.41 (m,1H), 7.35-7.10 (m,6H), 6.95 (m,1H), 6.68 (m,2H), 6.57 (m,1H), 3.44 (m,1H), 2.29 (s,3H), 1.77 (m,2H), 1.63 (m,2H), 1.52 (m,1H), 1.40-1.00 (m,5H)

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: The title compound crystallized on the addition of water to the reaction mixture. Filtration, washing (water), and drying afforded a pure crystalline product.

5 Mp: 158.3-159.8 °C

^1H NMR (DMSO- d_6): δ 8.34 (s,1H), 8.04 (d,1H), 7.79 (s,1H), 7.42 (m,1H), 7.10-7.34 (m,6H), 6.96 (m,1H), 6.67 (m,2H), 6.57 (m,1H), 3.07 (m,2H), 2.29 (s,3H), 1.02 (t,3H)

Example 3

10 1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-phenylurea (Compound 103)

General procedure: 1, except the reaction mixture was heated to 100 °C for 4 h

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Phenyl isocyanate

Solvent for the reaction: Pyridine

15 Purification: Crystallization from Et₂O

Mp: 163-166.8 °C

^1H NMR (DMSO- d_6): δ 9.15 (s,1H), 8.43 (s,1H), 8.13 (s,1H), 8.09 (d,1H), 7.10-7.50 (m,11H), 7.05 (m,1H), 6.96 (m,1H), 6.75 (d,1H), 6.63 (dd,1H), 2.28 (s,3H)

20 Example 4

1-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 104)

General procedure: 1, except the reaction mixture was heated to 100 °C for 4 h

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Butyl isocyanate

25 Solvent for the reaction: Toluene

Purification: Chromatography using EtOAc/pentane 3:7 as eluant followed by crystallization from Et₂O

Mp: 104-106 °C

30 ^1H NMR (DMSO- d_6): δ 8.35 (s,1H), 8.04 (d,1H), 7.80 (s,1H), 7.41 (m,1H), 7.08-7.34 (m,6H), 6.97 (m,1H), 6.70 (t,1H), 6.66 (d,1H), 6.57 (dd,1H), 3.05 (m,2H), 2.29 (s,3H), 1.20-1.40 (m,4H), 0.86 (t,3H)

Example 5

35 1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(4-methylphenylsulfonyl)urea (Compound 105)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: p-Toluenesulfonyl isocyanate

Solvent for the reaction: Toluene

- 5 Purification: The product was filtered off and washed with Et₂O to afford the title compound.

Mp: 180-185 °C

- ¹³C NMR (DMSO-d₆): δ 195.3, 150.3, 149.0, 143.9, 139.1, 136.7, 136.4, 133.9, 133.4, 133.4, 131.0, 130.7, 129.5, 129.3, 129.2, 128.8, 127.2, 126.4, 126.3, 125.6, 125.5, 10 124.1, 120.5, 114.7, 111.4, 20.9, 19.7

Example 6

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(phenylsulfonyl)urea (Compound 106)

- 15 General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Benzenesulfonyl isocyanate

Solvent for the reaction: Toluene

- 20 Purification: The product was filtered off and washed with Et₂O to afford the title compound.

Mp: 196-201 °C

- ¹³C NMR (DMSO-d₆): δ 195.3, 150.3, 139.6, 139.1, 136.4, 133.8, 133.7, 133.4, 131.7, 131.0, 130.7, 130.3, 129.3, 129.0, 128.8, 128.4, 127.2, 126.4, 126.4, 125.6, 125.5, 124.1, 120.5, 116.3, 114.7, 111.4, 19.7

25

Example 7

1-*tert*-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 107)

General procedure: 1, except the reaction mixture was heated to 50 °C for 6 h

- 30 Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: *tert*-Butyl isocyanate

Solvent for the reaction: Pyridine

Purification: The title compound crystallized on the addition of water to the reaction mixture. Filtration, washing (water), and drying afforded a pure crystalline product.

- 35 Mp: 159-161 °C

^1H NMR (DMSO- d_6): δ 8.32 (s,1H), 8.05 (d,1H), 7.73 (s,1H), 7.07-7.46 (m,7H), 6.95 (m,1H), 6.67 (d,1H), 6.60 (s,1H), 6.57 (dd,1H), 2.29 (s,3H), 1.26 (s,9H)

Example 8

- 5 1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-*iso*-propylurea (Compound 108)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: *iso*-Propyl isocyanate

- 10 Solvent for the reaction: Toluene

Purification: Chromatography using EtOAc/pentane 3:7 as eluant followed by crystallization from water

Mp: 103-106 °C

- 15 ^1H NMR (DMSO- d_6): δ 8.34 (s,1H), 8.07 (d,1H), 7.74 (s,1H), 7.42 (m,1H), 7.10-7.35 (m,6H), 6.95 (m,1H), 6.66 (m,2H), 6.56 (dd,1H), 3.71 (m,1H), 2.29 (s,3H), 1.06 (d,6H)

Example 9

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-propylurea (Compound 109)

General procedure: 1

- 20 Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Propyl isocyanate

Solvent for the reaction: Pyridine

- 25 Purification: Crystallization from Et₂O

Mp: 133-135 °C

- 30 ^{13}C NMR (DMSO- d_6): δ 195.2, 155.1, 150.7, 139.4, 136.3, 136.2, 133.5, 130.9, 130.5, 128.6, 128.3, 126.1, 125.8, 125.5, 121.8, 120.3, 114.7, 111.4, 40.8, 22.8, 19.6, 11.3

Example 10

1-Methyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 110)

- 35 General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Methylisocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from Et₂O

- 35 Mp: 154-155 °C

^1H NMR ($\text{DMSO}-d_6$): δ 8.35 (s,1H), 8.01 (d,1H), 7.84 (s,1H), 7.40 (m,1H), 7.09-7.35 (m,6H), 6.97 (m,1H), 6.68 (d,1H), 6.59 (m,2H), 2.61 (d,3H), 2.29 (s,3H)

Example 11

5 Ethyl 3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionate
(Compound 111)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Ethyl 3-isocyanatopropionate

10 Solvent for the reaction: Pyridine

Purification: Chromatography using EtOAc/pentane 3:2 as eluant to give the title compound as a syrupy

^{13}C NMR (CDCl_3): δ 196.7, 172.9, 156.3, 148.8, 139.2, 137.8, 135.0, 133.6, 133.0, 131.9, 131.3, 130.9, 129.6, 128.5, 125.4, 125.4, 124.2, 123.8, 116.4, 112.7, 60.9, 36.0, 34.7, 20.4, 14.1

Example 12

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 112)

20 General procedure: 1

Starting compound II: 4-[(2-Amino-4-bromo-phenyl)amino]-2-chloro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

25 Purification: Crystallization from a mixture of EtOAc/pentane 1:1

Mp: 125-127 °C

^{13}C NMR (CDCl_3): δ 197.5, 155.8, 149.2, 138.9, 137.7, 135.2, 135.0, 133.6, 131.4, 131.2, 129.8, 129.7, 128.2, 126.8, 126.2, 125.5, 125.0, 118.7, 116.1, 112.3, 35.2, 20.5, 15.2

30

Example 13

3-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionic acid
(Compound 113)

Ethyl 3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido) propionate

35 (Compound 111, 6.25 mmol) and K_2CO_3 (9.4 mmol) was stirred in a mixture of MeOH (25 ml) and water (8 ml) for 4 h at ambient temperature. More water (13 ml) was added and

the reaction mixture was stirred overnight. The reaction mixture was poured into EtOAc and water. pH was adjusted to approximately 4 with glacial acetic acid. The organic phase was separated, washed with water and brine, then dried (MgSO_4), filtered and concentrated *in vacuo* to afford a weakly coloured oily crude product. Purification was done by chromatography using $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{CH}_3\text{COOH}$ 250:10:1 as eluant to afford the title compound.

^{13}C NMR (CDCl_3): δ 197.5, 176.3, 157.0, 148.9, 138.9, 137.9, 134.9, 133.5, 132.8, 131.7, 131.3, 131.1, 129.8, 128.4, 125.6, 125.5, 124.4, 123.9, 116.3, 112.6, 35.8, 34.5, 20.7, 20.5

Example 14

1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-5-fluoro-phenyl]urea
(Compound 114)

General procedure: 1

Starting compound II: 2-Chloro-4-[(4-fluoro-2-aminophenyl)amino]-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Chromatography using EtOAc/pentane 1:2 as eluant to give the title compound as a syrupy

^{13}C NMR (CDCl_3): δ 197.2, 162.9, 159.6, 155.1, 150.2, 138.9, 137.8, 137.4, 137.2, 135.1, 133.6, 131.4, 131.1, 129.7, 128.4, 128.0, 127.9, 125.5, 124.7, 115.6, 111.8, 110.1, 109.8, 108.2, 107.9, 35.2, 20.5, 15.1

Example 15

1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-*N*-methyl-phenylamino]-5-fluoro-phenyl]urea
(Compound 115)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromo-*N*-methyl-phenylamino)-2-chloro-2'-methylbenzophenone

Purification: Chromatography using EtOAc/pentane 1:5 as eluant

^{13}C NMR (CDCl_3): δ 197.6, 162.2, 154.8, 152.8, 139.4, 138.8, 137.1, 135.4, 133.9, 31.3, 130.9, 129.6, 129.0, 128.5, 126.3, 125.5, 114.9, 111.1, 109.3, 107.1, 39.4, 34.9, 20.3, 14.8

Example 16

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-*n*-butyl-2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 116)

General procedure: 1

5 Starting compound II: 4-(2-Amino-4-bromophenylamino)-4'-*n*-butyl-2-chloro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

10 ^{13}H NMR (DMSO- d_6): δ 8.36 (m, 1H), 8.27 (s, 1H), 7.94 (s, 1H), 7.24 (d, 1H), 7.2-7.0 (m, 5H), 6.86 (t, 1H), 6.69 (d, 1H), 6.58 (dd, 1H), 3.08 (m, 2H), 2.59 (t, 2H), 2.32 (s, 3H), 1.56 (m, 2H), 1.30 (m, 2H), 1.15-0.80 (m, 6H)

Example 17

15 1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,5-dimethylbenzoyl)-phenylamino]phenyl]urea
(Compound 117)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-2',5'-dimethylbenzophenone

Starting compound III: Ethyl isocyanate

20 Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

25 ^{13}C NMR (DMSO- d_6): δ 195.5, 154.8, 150.3, 139.2, 138.1, 134.7, 133.6, 133.5, 133.4, 131.4, 131.0, 129.1, 127.8, 127.4, 126.5, 124.2, 121.9, 118.4, 115.1, 111.6, 33.9, 20.4, 19.4, 15.2

Example 18

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(3-chloro-2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 118)

General procedure: 1

30 Starting compound II: 4-(2-Amino-4-bromophenylamino)-2,3'-dichloro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

35 ^{13}C NMR (DMSO- d_6): δ 193.8, 154.6, 151.0, 142.3, 138.0, 134.5, 134.4, 134.1, 133.2, 130.7, 127.9, 127.2, 127.0, 126.5, 124.9, 124.1, 121.9, 118.6, 115.2, 111.5, 33.8, 16.6, 15.1

Example 19

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-ethoxy-2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 119)

5 General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-4'-ethoxy-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

10 Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO- d_6): δ 194.5, 160.8, 154.8, 149.6, 140.6, 138.0, 132.9, 132.5, 132.3, 130.6, 128.2, 127.8, 127.6, 124.2, 121.9, 118.2, 117.3, 114.7, 111.8, 111.1, 63.3, 33.9, 20.8, 15.2, 14.6

Example 20

1-Ethyl-3-[5-bromo-2-[3-ethoxy-4-(2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 120)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-ethoxy-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO- d_6): δ 195.2, 160.2, 154.7, 151.9, 143.1, 137.4, 134.2, 132.3, 129.9, 128.6, 128.3, 127.1, 126.3, 125.0, 124.1, 122.2, 118.0, 117.5, 106.6, 97.2, 62.9, 33.8, 19.2, 15.1, 13.5

Example 21

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-chloro-2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 121)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2,4'-dichloro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO- d_6): δ 194.1, 154.6, 150.6, 139.0, 138.0, 135.1, 133.6, 133.5, 130.6,

130.4, 127.8, 127.2, 125.9, 125.6, 124.1, 121.8, 118.4, 114.9, 111.6, 45.0, 33.8, 19.4, 15.1

Example 22

- 5 1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,3-dimethylbenzoyl)-phenylamino]phenyl]urea
(Compound 122)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-2',3'-dimethylbenzophenone

- 10 Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

¹³C NMR (DMSO-d₆): δ 195.6, 154.6, 150.5, 140.3, 138.0, 137.4, 134.2, 134.0, 133.7, 131.5, 127.8, 127.2, 126.0, 125.6, 125.1, 124.1, 121.8, 118.4, 115.1, 111.4, 33.8, 19.6, 16.0, 15.1

Example 23

1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(4-methoxy-2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 123)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-fluoro-4'-methoxy-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

¹³C NMR (DMSO-d₆): δ 192.0, 162.3, 160.8, 154.8, 152.2, 138.9, 138.0, 133.1, 132.3, 131.1, 127.8, 127.6, 124.2, 122.0, 118.4, 116.6, 116.4, 110.7, 109.8, 100.1, 55.3, 33.9, 20.2, 15.2

Example 24

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,4,5-trimethylbenzoyl)-phenylamino]phenyl]urea
(Compound 124)

General procedure: 1

Starting compound II: 4'-(2-Amino-4-bromophenylamino)-2'-chloro-2,4,5-trimethylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO- d_6): δ 195.2, 154.7, 149.9, 139.6, 137.9, 136.4, 134.2, 133.2, 133.0, 132.4, 130.3, 127.6, 127.5, 127.1, 124.1, 121.8, 118.2, 114.8, 111.6, 33.8, 19.4, 19.2, 18.6, 15.1

5

Example 25

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-fluoro-2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 125)

General procedure: 1

10 Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-4'-fluoro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

15 ^{13}C NMR (DMSO- d_6): δ 194.1, 162.9, 154.6, 150.3, 140.4, 138.0, 135.6, 133.3, 131.6, 127.7, 127.3, 126.4, 124.1, 121.8, 118.3, 117.7, 114.8, 112.4, 111.6, 33.8, 19.8, 15.1

Example 26

1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea
(Compound 126)

General procedure: 1

20 Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-fluoro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

25 Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO- d_6): δ 192.9, 163.0, 154.8, 153.0, 140.7, 138.0, 135.0, 133.3, 130.6, 129.9, 128.0, 127.2, 125.5, 124.2, 122.0, 118.6, 115.5, 109.9, 100.1, 33.9, 19.3, 15.2

30 Example 27. Tablet containing compound 102

Compound 102 (active substance)	50 mg
Lactose	125 mg
Starch	12 mg
35 Methyl cellulose	2 mg
Sodium carboxymethyl cellulose	10 mg
Magnesium stearate	1 mg

The active substance, lactose and starch are mixed to a homogeneous state in a suitable mixer and moistened with a 5 per cent aqueous solution of methyl cellulose 15 cps. The mixing is continued until granules are formed. If necessary, the wet granulation is passed through a suitable screen and dried to a water content of less than 1% in a suitable drier, e.g. fluid bed or drying oven. The dried granules are passed through a 1 mm screen and mixed to a homogeneous state with sodium carboxymethyl cellulose. Magnesium stearate is added, and the mixing is continued for a short period of time. Tablets with a weight of 200 mg are produced from the granulation by means of a suitable tableting machine.

Example 28. Formulation for injection containing compound 102.

Compound 102 (active substance)	1%
Sodium chloride	q.s.
Ethanol	10%
Water for injection to make	100%

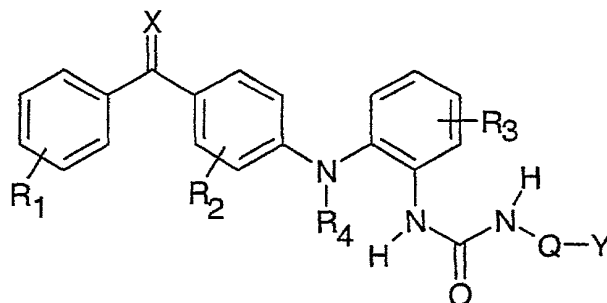
The active substance is dissolved in ethanol (10%) then water for injection made isotonic with sodium chloride is added to make 100%. The mixture is filled into ampoules and sterilized.

Example 29. Cream formulation containing compound 101.

Compound 101 (10 g) was dissolved in Octyldodecyl myristate (250g) to form Part A. Methylparaben (1 g) and propylparaben (0.2 g) were dissolved in phenoxyethanol (6 g) and mixed with a 0.025 M Phosphate buffer pH = 7.5 (632,8 g) to form Part B. Cetostearyl alcohol (50 g) and ARLACEL 165® (50 g) was melted in a vessel at 70° to 80 °C. Part A was added and heated to 60-70°C. The aqueous phase was likewise heated to 60-70 °C and slowly added to the melted oil phase under high speed stirring. The homogenized components were cooled to room temperature.

CLAIMS

1. A compound of the formula I



I

wherein R_1 independently represents one or more, same or different substituents selected from the group consisting of halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3) alkyl, (C_2-C_3) olefinic group, (C_1-C_3) alkoxy, (C_1-C_3) alkylthio, (C_1-C_6) alkylamino, (C_1-C_3) alkoxycarbonyl, cyano, carbamoyl, phenyl and nitro, provided that when R_1 represents one substituent, it is in the ortho position, and when R_1 represents more than one substituent, at least one R_1 substituent is in the ortho position; R_2 is one substituent in the ortho position, said substituent being selected from the group consisting of hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3) alkyl, (C_2-C_3) olefinic group, (C_1-C_3) alkoxy, (C_1-C_3) alkylthio, (C_1-C_6) alkylamino, (C_1-C_3) alkoxycarbonyl, cyano, carbamoyl, phenyl and nitro;

R_3 represents hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3) alkyl, (C_2-C_3) olefinic group, (C_1-C_3) alkoxy, (C_1-C_3) alkylthio, (C_1-C_6) alkylamino, (C_1-C_3) alkoxycarbonyl, phenyl, cyano, carboxy, or carbamoyl;

R_4 represents hydrogen, (C_1-C_3) alkyl, or allyl;

Q represents a bond, $-SO_2-$, or $-C(R_6)(R_7)(-O-C=O)-$, in which formula R_6 and R_7 independently represent hydrogen, trifluoromethyl, or (C_1-C_4) alkyl;

Y represents (C_1-C_{15}) alkyl, (C_2-C_{15}) olefinic group, (C_3-C_{10}) carbocyclic group, or phenyl, any of which is optionally substituted by one or more, same or different substituents represented by the formula R_5 ; or Y represents a group of

formula $-(Z-O)_n-Z$, where Z is a (C_1-C_3) alkyl and n is an integer > 1 , and no continuous linear sequence of atoms in the group Y exceeds 15;

R_5 represents halogen, hydroxy, mercapto, trifluoromethyl, (C_1-C_4) alkyl, amino, (C_1-C_3) alkoxy, (C_1-C_3) alkylthio, (C_1-C_6) alkylamino, (C_1-C_3) alkoxycarbonyl, cyano, azido, nitro, $-COOH$, $-CONH_2$, $-CONHR'$, or $-CONRR'$ wherein R and R' stands for (C_1-C_3) alkyl;

X represents oxygen or sulphur,

or a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof.

2. A compound according to claim 1 wherein independently

- R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C_1-C_2) alkyl, (C_2-C_3) alkenyl, (C_1-C_3) alkoxy, (C_1-C_3) alkoxycarbonyl, or cyano.
- R_2 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C_1-C_2) alkyl, (C_2-C_3) alkenyl, (C_1-C_3) alkoxy.
- R_3 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, (C_1-C_3) alkyl, (C_2-C_3) alkenyl, (C_1-C_3) alkoxy, (C_1-C_3) alkoxycarbonyl, cyano, or carboxy.
- R_4 represents hydrogen, (C_1-C_2) alkyl, or allyl.
- X represents oxygen.
- Q represents a bond or $-SO_2-$.

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- Y represents (C₁-C₆)alkyl; (C₂-C₆)alkenyl; (C₃-C₆)cycloalkyl; (C₅-C₈)cycloalkene group; or phenyl; any of which is optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R₅, R₅ representing fluoro, chloro, bromo, hydroxy, amino, (C₁-C₂)alkoxy, (C₁-C₄)alkylamino, (C₁-C₃)alkoxycarbonyl, cyano, azido, -COOH, -CONH₂, -CONHR', or -CONR'R' wherein R' represents (C₁-C₂)alkyl.

3. A compound according to any one of the preceding claims wherein R₁ represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, methyl, or methoxy.

4. A compound according to any one of the preceding claims wherein R₁ is methyl and R₂ is Cl.

5. A compound according to claim 1 selected from the group consisting of
- 1-Cyclohexyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 101),
 - 1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 102),
 - 1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-phenylurea (Compound 103),
 - 1-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 104),
 - 1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-*iso*-propylurea (Compound 108),
 - 1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-propylurea (Compound 109),
 - 1-Methyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 110),
 - 1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 112),
 - 1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-5-fluoro-phenyl]urea (Compound 114),
 - 1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,5-dimethylbenzoyl)-phenylamino]phenyl]urea (Compound 117),

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1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-chloro-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 121),

1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(4-methoxy-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 123),

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,4,5-trimethylbenzoyl)-phenylamino]phenyl]urea (Compound 124),

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-fluoro-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 125),

1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 126),

and salts thereof with pharmaceutically acceptable acids, hydrates and solvates.

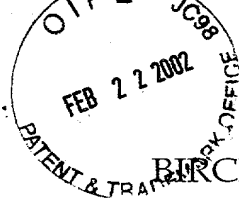
6. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 5 together with a pharmaceutically acceptable carrier and optionally together with a second active ingredient optionally selected from the group consisting of glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticholinergic agents, methyl xanthines, β -adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).
7. Use of a compound according to any one of claim 1 to 5 for the preparation of a medicament for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, osteoporosis and acne.
8. A method for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, osteoporosis and acne, characterised in administering to a patient suffering from at least one of said diseases an effective amount of one or more compounds according to any one of claims 1 to 5 as an active ingredient alone, or if necessary together with a pharmaceutically acceptable carrier, and, optionally, a second active ingredient optionally selected from the

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group consisting of glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticholinergic agents, methyl xanthines, β -adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

9. A method of treatment according to the preceding claim comprising administering to a mammal in need of systemic treatment a suitable dose of a compound of formula I of from 0.1 to 200 mg/kg bodyweight, preferably a dose of from 0.2 to 50 mg/kg of mammal bodyweight one or more times daily.

202220-060300T



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BIRCH, STEWART, KOLASCH & BIRCH, LLP

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COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT AND DESIGN APPLICATIONS

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Insert Title:

AMINO BENZOPHENONES AS INHIBITORS OF IL-1 β AND TNF- α

Fill in Appropriate
Information -
For Use Without
Specification
Attached:

the specification of which is attached hereto. If not attached hereto,

the specification was filed on January 15, 2002 as

United States Application Number _____;

and amended on January 15, 2002 (if applicable) and/orthe specification was filed on July 11, 2000 as PCTInternational Application Number PCT/DK00/00387; and wasamended on June 20, 2001 (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representative or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Insert Priority
Information:
(if appropriate)

Prior Foreign Application(s)

Priority Claimed

60/144,062
(Number)US
(Country)July 16, 1999
(Month/Day/Year Filed)☒ Yes ☐ No

(Number)

(Country)

(Month/Day/Year Filed)

☐ Yes ☐ No

(Number)

(Country)

(Month/Day/Year Filed)

☐ Yes ☐ No

(Number)

(Country)

(Month/Day/Year Filed)

☐ Yes ☐ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional applications(s) listed below.

Insert Provisional
Application(s):
(if any)

(Application Number)

(Filing Date)

(Application Number)

(Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More than 12 Months (6 Months for Designs) Prior to the Filing Date of This Application:

Country

Application Number

Date of Filing (Month/Day/Year)

Insert Requested
Information:
(if appropriate)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States and/or PCT application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States and/or PCT application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Insert Prior U.S.
Application(s):
(if any)

(Application Number)

(Filing Date)

(Status - patented, pending, abandoned)

(Application Number)

(Filing Date)

(Status - patented, pending, abandoned)

FEB 22 2002

Attorney Docket No. 3893-0139P

I hereby appoint the practitioners at CUSTOMER NO. 2292 as my attorneys or agents to prosecute this application and/or international application based on this application and to transact all business in the United States Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the practitioners, unless the inventor(s) or assignee provides said practitioners with a written notice to the contrary:

Send Correspondence to:

BIRCH, STEWART, KOLASCH & BIRCH, LLP or **CUSTOMER NO. 2292**P.O. Box 747 • Falls Church, Virginia 22040-0747Telephone: (703) 205-8000 • Facsimile: (703) 205-8050

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of First
or Sole Inventor:
Insert Name of
Inventor
Insert Date This
Document is Signed

Insert Residence
Insert Citizenship

Insert Post Office
Address

Full Name of Second
Inventor, if any:
see above

Full Name of Third
Inventor, if any:
see above

Full Name of Fourth
Inventor, if any:
see above

Full Name of Fifth
Inventor, if any:
see above

Full Name of Sixth
Inventor, if any:
see above

GIVEN NAME/FAMILY NAME <u>Erik Rytter OTTOSEN</u>	INVENTOR'S SIGNATURE <i>Erik Rytter</i>	DATE* <u>5/02/2002</u>
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MAILING ADDRESS (Complete Street Address including City, State & Country)		
GIVEN NAME/FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
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